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Conservative versus immunosuppressive treatment of patients with idiopathic membranous nephropathy[1]

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Conservative versus immunosuppressive treatment of patients with idiopathic membranous nephropathy.

Background. Treatment of idiopathic membranous glomerulonephritis (MGN) is a controversial issue. Whereas some authors recommend early immunosuppressive treatment of all patients with nephrotic syndrome, others do not support aggressive therapies, based on the spontaneous long-term favorable outcome of most patients. However, 20 to 50% of untreated patients develop progressive renal insufficiency.

Methods. All of the patients with biopsy-proven MGN who developed renal insufficiency at our Hospital during the period of 1975 to 2000 were studied. Selected patients ($N = 39$) were separated into two groups according to the two different therapeutic policies followed at our department: a conservative approach during the first period, 1975 to 1989 (group I, $N = 20$), and a course of immunosuppressive therapy (oral prednisone for six months and concurrent oral chlorambucil, 0.15 mg/kg/day, during the first 14 weeks) during the second period, 1990 to 2000 (group II, $N = 19$).

Results. There were no significant differences between both groups at the time of renal biopsy, nor at the onset of renal function decline. All group I patients showed a progressive renal insufficiency; at the end of the follow-up 13 patients (65%) were on chronic dialysis, 2 (10%) showed advanced renal failure, and 5 (25%) had died. In contrast, most of group II patients showed an improvement or stabilization of serum creatinine (S_{Cr}; 2.3 ± 0.9 mg/dL at onset of treatment, 2 ± 1.5 mg/dL at the end of follow-up) together with decreased proteinuria (11.2 ± 3.3 vs. 5.2 ± 6.7 g/24 h). At the end of the follow-up 58% of group II patients had a S_{Cr} value ≤1.5 mg/dL and 36% showed a complete or partial remission, whereas no patient in group I showed remission. After four years of follow-up the probability of renal survival without dialysis was 55% in group I and 90% in group II ($P < 0.001$), and after seven years the renal survival was 20% and 90%, respectively ($P < 0.001$). Side effects of immunosuppressive treatment were uncommon but severe, as two patients suffered *Pneumocystis carinii* pneumonia.

Conclusion. A course of immunosuppressive treatment administered early at the onset of renal function decline induces a favorable effect in most of patients with MGN and deteriorating renal function. Untreated patients progressed without exception toward advanced renal failure.

Treatment of membranous glomerulonephritis (MGN) remains a very controversial issue [1]. Whereas some authors recommend a conservative approach, given the high incidence of spontaneous remissions and the long-term good prognosis of most of the patients [2], other authorities administer a course of immunosuppressive drugs to all the patients with nephrotic syndrome, since several prospective and controlled studies have demonstrated the superiority of this regimen compared with the conservative approaches [3–5]. This latter aggressive management of MGN has been criticized because many patients who probably would evolve into spontaneous remissions are exposed to the risks of immunosuppressive therapies. On the other hand, the conservative approach without the attempt of immunosuppressive treatment would leave a considerable percentage of patients (ranging from 20% to more than 50% in some studies) with a progressive derangement of renal function [6–11].

To resolve this contradiction, several authors have proposed a more flexible approach, selecting only those patients at highest risk for progressive disease for immunosuppressive therapies. Several clinical and biochemical parameters that would define a bad prognosis (men over the age of 50 years, sustained massive proteinuria values, elevation of serum creatinine) have been proposed to establish such a selection [12–16]. Among these, the presence of deteriorated renal function, at presentation or throughout the evolution of the disease, appears to be the strongest clinical predictor of progression to advanced renal failure, since the spontaneous recovery of normal renal function (once the functional factors in the setting of nephrotic syndrome and diuretic therapy are excluded) is the exception in MGN.

Some studies have reported a beneficial effect of im-

[1] **See Editorial by Cattran, p. 349.**

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munosuppressive treatments in MGN with deteriorating renal function [17–25]. The present study reports our experience with MGN patients who develop progressive renal failure. Until 1990 we maintained a conservative approach, avoiding the use of steroids or cytotoxic drugs even in patients showing a progressive decline in renal function. Thus, during the period of 1975 to 1989, 67 patients with idiopathic MGN were studied, 20 of whom (29.8%) showed progressive renal insufficiency. Since 1990, we have decided to administer a course of immunosuppressive treatment (steroids plus chlorambucil) to all MGN patients presented with impaired renal function. Thus, during the period of 1990 to 2000, 19 patients out of a total of 55 (34.5%) idiopathic MGN received this treatment because of the appearance of renal insufficiency. The outcomes of both cohorts are compared: group I was managed conservatively (period 1975 to 1989) and group II was treated with immunosuppressive drugs (period 1990 to 2000).

METHODS

All biopsy-proven patients with idiopathic MGN who developed progressive renal insufficiency assessed at our Hospital in the period of 1975 to 2000 were included in this study. The medical records of all the patients diagnosed as having MGN were reviewed in order to identify those showing renal insufficiency. Excluded from the study were those patients with systemic lupus erythematosus or any other systemic disease, diabetes mellitus, chronic infectious diseases (including infections by hepatitis B and C viruses and HIV), drug-induced MGN, hematologic diseases, and every patient in whom a diagnosis of secondary MGN has been established during the study.

Renal insufficiency was defined as a serum creatinine (S_{Cr}) $\geq$1.5 mg/dL together with a creatinine clearance (C_{Cr}) $\leq$60 mL/m, in at least three consecutive determinations. Renal insufficiency was progressive in all the included patients. Before considering progressive renal insufficiency attributable to the glomerular disorder, functional factors such as overzealous diuretic therapy, and angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) were carefully ruled out. When clinically suspected (flank pain, hematuria, very sudden onset of renal insufficiency, pulmonary emboli, suggestive radiological findings) renal vein thrombosis was always ruled out.

THERAPEUTIC APPROACHES

First period (1975 to 1989)

During these years a conservative attitude towards the treatment of patients with idiopathic MGN was maintained, and immunosuppressive treatments were avoided even in those patients showing progressive renal insufficiency. Salt restriction, diuretic therapy, lipid-lowering agents and antihypertensive drugs (including ACE inhibitors as antiproteinuric agents) were the basis of treatment. In those patients showing a decline in renal function, no specific changes in the treatment were adopted, except the reduction or withdrawal of drugs (mainly diuretics and ACE inhibitors) that could play a role in renal function derangement.

Second period (1990 to 2000)

A retrospective analysis of our patients with MGN performed in 1989 showed a uniform evolution toward advanced renal failure in every patient with a decline in renal function. Therefore, we decided to change our policy, administering a course of immunosuppressive treatment to every new patient with idiopathic MGN in whom renal insufficiency of recent onset (defined by the above criteria) was detected. Immunosuppressive treatment consisted of oral prednisone for six months starting with 1 mg/kg/day for the first month, 0.5 mg/kg/day for the second month and 0.5 mg/kg/every other day from third to sixth months, accompanied by simultaneous oral chlorambucil (0.15 mg/kg/day) during the first 14 weeks (3½ months). Prophylactic treatment with trimethoprim-sulfamethoxazole (3 times/week for 6 months since the beginning of the prednisone/chlorambucil treatment) was instituted in 1994, after the appearance of *Pneumocystis carinii* pneumonia in two patients.

Treatment of patients with normal renal function was the same as before, that is, salt restriction, diuretics, lipid-lowering drugs, antihypertensive agents including the preferential use of ACE inhibitors because of their antiproteinuric effect. Again, in every patient showing a renal function decline, the reversible functional causes (such as diuretics and ACE inhibitors) were carefully ruled out before the patient initiated immunosuppressive therapy.

All of the included patients were biopsied at our Hospital and thereafter followed at regular intervals (every 1 to 3 months) at our outpatient clinic. The following data at the time of renal biopsy and at every visit were obtained from medical records and analyzed for the present study: age, gender, interval of time between the performance of renal biopsy and the appearance of renal insufficiency, blood pressure, S_{Cr}, C_{Cr}, and 24 hour proteinuria. The duration of follow-up between the appearance of renal insufficiency until the last visit, death or the onset of chronic dialysis was calculated in every case. All renal biopsies were processed by light microscopy, immunofluorescence and electron microscopy. The stage of MGN (stages I to IV) was reviewed in every case. The severity of interstitial fibrosis was graded semiquantitatively on a scale of 0 to 4, with 0 = none and 4 = severe.

Complete remission was defined as a proteinuria $\leq$0.5 g/24 h with normal serum albumin and normal renal

function. Partial remission was defined as a proteinuria between 0.5 and 2.5 g/24 h, or a decrease in proteinuria ≥50% from previous values together with a normal serum albumin and normal renal function. Nephrotic syndrome was defined as a proteinuria ≥3.5 g/24 h accompanied by hypoalbuminemia (≤3 g/dL). Mean arterial pressure (MAP) was calculated as the diastolic blood pressure plus one third of the pulse pressure.

Statistical analysis

For statistical analysis, the paired and unpaired Student *t* test and Mann-Whitney test were used where appropriate. Fisher's correction was applied when indicated. The study of data evolution throughout the study period was performed by the analysis of variance for repeated measurements (ANOVA). The cumulative probability of death or renal function survival without dialysis (censoring death without dialysis) was estimated by the Kaplan-Meier method. The values are expressed as mean ± SD. *P* values <0.05 were considered statistically significant.

Table 1. Clinical features of group I patients (conservative treatment) and group II (immunosuppressive treatment)

	Group I $N = 20$	Group II $N = 19$	*P*
Age[a] *years*	53 ± 16 *r* = 21–77	55 ± 20 *r* = 24–81	NS
Gender *M/F*	15/5 (75/25%)	11/8 (57/43%)	NS
S_{Cr}[a] *mg/dL*	1.4 ± 1.0 *r* = 0.7–5.3	1.4 ± 0.7 *r* = 0.8–4	NS
Proteinuria[a] *g/24 h*	6.9 ± 3.1 *r* = 1–13.2	8.9 ± 3.6 *r* = 4–15.6	NS
MAP[a] *mm Hg*	103 ± 12 *r* = 86–133	102 ± 13 *r* = 86–133	NS
Stage of MGN	I 2 (10%) II 15 (75%) III 3 (15%) IV 0	I 3 (15.7%) II 13 (68%) III 3 (15.7%) IV 0	NS
Interval between renal biopsy and the appearance of renal insufficiency *months*	10.8 ± 11.8 *r* = 0.1–49	14 ± 18.6 *r* = 0.1–65	
S_{Cr} *mg/dL* at the onset of immunosuppressive treatment		2.3 ± 0.94 *r* = 1.5–5.2	
Follow up[b] *months*	46.8 ± 37.5 *r* = 5–120	51.8 ± 36.5 *r* = 8–120	NS

[a] At the time of renal biopsy
[b] Follow-up defined as the interval between the appearance of renal insufficiency and last visit, death or onset of chronic dialysis

RESULTS

During the first period (1975 to 1989), 67 patients were diagnosed at our Hospital of idiopathic MGN. Twenty of them (29.8%; group I) showed renal insufficiency as described in the **Methods** section and were managed without immunosuppressive drugs. During the second period (1990 to 2000), 19 patients out of 55 cases of idiopathic MGN diagnosed at our Hospital developed renal insufficiency (34.5%; group II). The main clinical and analytical features of both groups are shown in Table 1. The interval between onset of the disease (appearance of edema, proteinuria detection) and the performance of renal biopsy was similar in both groups, ranging from 1 to 12 months. There were no significant differences in age, blood pressure, renal function or proteinuria at the time of renal biopsy. There was a majority of male patients in both groups (75% and 57%, without significant differences). With the exception of five patients in group I and four in group II, all the patients had normal renal function (S_{Cr} ≤1.5 mg/dL and C_{Cr} ≥60 mL/m) at the time of renal biopsy. Seventy-five percent of group I patients and 78% of group II showed nephrotic syndrome at renal biopsy. There were no differences in the histological stage of MGN, as most of the patients in both groups (75% and 68%, respectively) showed stage II of the disease. The severity of interstitial fibrosis was 1.2 ± 0.3 (r = 1 to 2) in group I and 1.3 ± 0.4 (r = 1 to 2) in group II.

There were no significant differences in the time elapsed between renal biopsy and the appearance of renal insufficiency: 10.8 ± 11.8 months in group I (range 0 to 49 months) and 14 ± 18.6 months in group II (range 0 to 65 months). Except for four (20%) patients in group I and four (21%) in group II, renal function decline started within the first two years of evolution after renal biopsy. Proteinuria in the nephrotic range was observed in every patient of both groups coincidental with the onset of renal function derangement (8.6 ± 3.4 g/24 h, r = 3.8 to 14 in group I, and 11.2 ± 3.3, r = 7 to 21 in group II).

Renal function decline continued progressing toward advanced renal failure in all the patients from group I, who received a conservative management (Fig. 1). After a mean follow up of 46.8 ± 37.5 months (r = 5 to 120 months) S_{Cr} had increased from 2 ± 0.8 mg/dL (r = 1.5 to 5.3 mg/dL) to 6.7 ± 2.8 (r = 1.9 to 12.6 mg/dL; $P < 0.001$; Fig. 2). Proteinuria in the nephrotic range was observed in every patient during the progression of renal failure; however, when renal insufficiency was severe there was a tendency to a decrease in proteinuria in relationship with advanced renal failure (Fig. 2). At the end of the follow-up period (Table 2), 13 patients of this group (65%) were on chronic dialysis, 2 (10%) showed advanced renal failure and 5 (25%) had died, 2 because of sepsis, 1 with ischemic heart disease, 1 from stroke and, finally, 1 in unrecorded circumstances. All five patients who died also showed a progressive renal insufficiency. No complete or partial remissions, as defined in the **Methods** sections, were observed in any patient of this group.

By contrast, renal function remained stable or improved in a majority of group II patients who received a course of immunosuppressive treatment. Mean S_{Cr} at the onset of treatment was 2.3 ± 0.9 mg/dL (r = 1.5 to

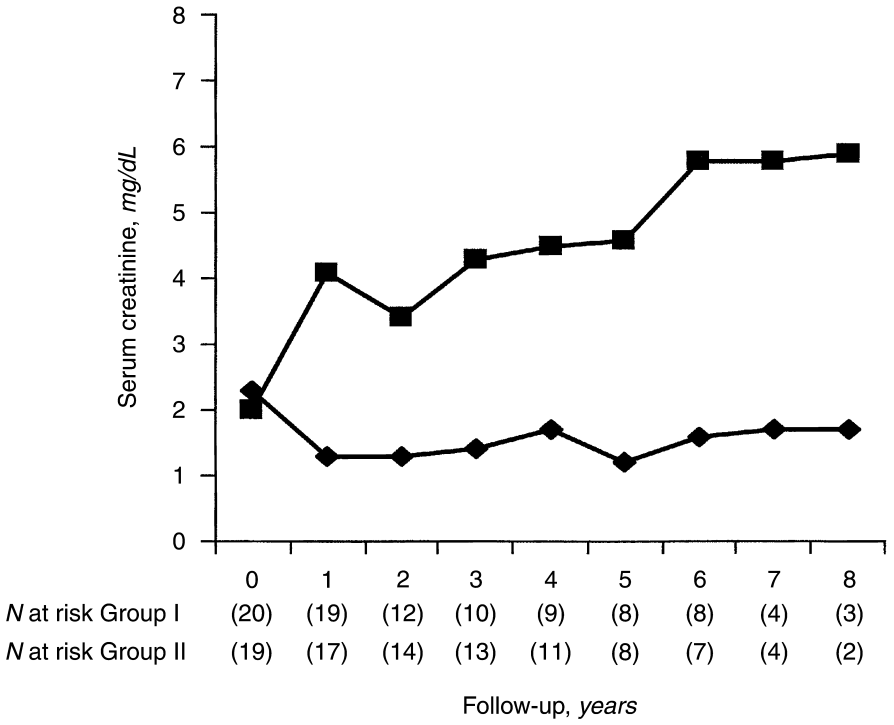

Fig. 1. Evolution of serum creatinine (S_{Cr}) in group I (conservative management; ■) and group II (immunosuppressive treatment; ◆) patients. Numbers in brackets represent the number of patients at risk at every period.

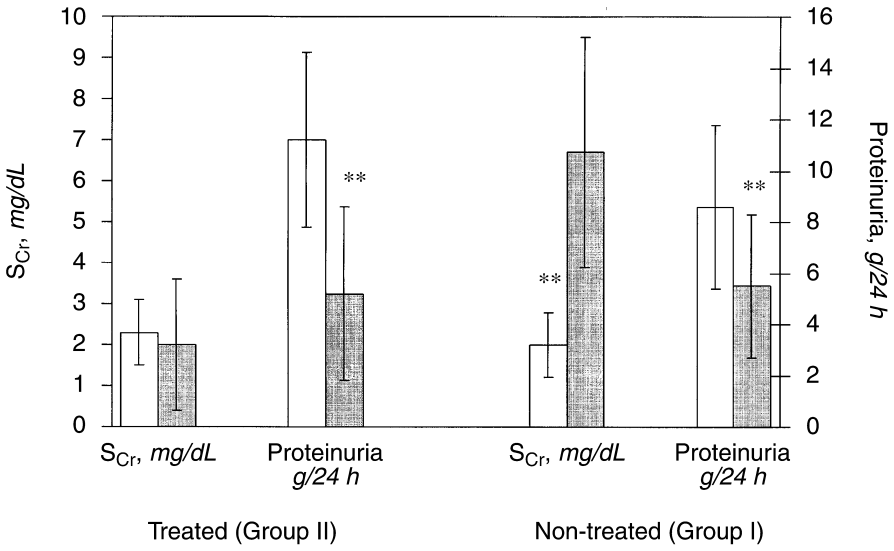

Fig. 2. Serum creatinine (S_{Cr}) and proteinuria values at the onset of renal function worsening (□) and at the end of follow-up (■) in treated (group II) and non-treated (group I) patients.

5.2 mg/dL) and mean proteinuria 11.2 ± 3.3 g/24 h (r = 7 to 21 g/24 h). Both S_{Cr} and proteinuria showed a rapid and significant decrease after the introduction of prednisone and chlorambucil treatment. After two months of treatment S_{Cr} had decreased to 1.6 ± 0.4 mg/dL ($P <$ 0.01) and at the completion (6 months) of treatment it was 1.2 ± 0.4 mg/dL ($P < 0.01$). Proteinuria also showed a significant decrease by the fourth month of treatment (6.8 ± 5.2 g/24 h; $P < 0.05$) and at the end of treatment it was 5.6 ± 3.5 g/24 h ($P < 0.01$ with respect to values at the onset of treatment). The mean follow-up of group II patients was 51.8 ± 36.5 months (r = 8 to 120 months). The mean S_{Cr} value at the end of follow-up was 2 ± 1.5 mg/dL (r = 0.7 to 6.2 mg/dL), with no significant difference with respect to values at the onset of treatment, whereas proteinuria remained significantly lower (5.2 ± 6.7 g/24 h, r = 0 to 27 g/24 h; Fig. 2). At the end of the follow-up (Table 2), five patients (26%) of this group were in complete remission, two (10%) in partial remission, and five (26%) showed a normal renal

Table 2. Clinical status at the end of follow-up

	Group I $N = 20$ Non-treated	Group II $N = 19$ Treated
Complete remission	0	5 (26%)
Partial remission	0	2 (10.5%)
Proteinuria >2.5 g/24 h with normal renal function	0	5 (26%)
Chronic renal failure	2 (10%)	4 (21%)
Dialysis	13 (65%)	2 (10%)
Death	5 (25%)	2 (10%)

function with proteinuria ≥2.5 g/24 h. Four patients (21%) showed chronic renal insufficiency, two (10%) were on chronic dialysis and two patients (10%) had died, one of them because of a stroke despite a normal renal function, and the other because of sepsis with a S_{Cr} of 2.5 mg/dL.

There were no significant differences in blood pressure at the onset of renal function deterioration (MAP of group I 107 ± 15 mm Hg, group II 100 ± 10 mm Hg) or during the first months of follow-up (after 6 months of follow-up, the MAP of group I was 103 ± 12 mm Hg and that of group II, 98 ± 12 mm Hg). Since the first year of follow-up, group I showed a significantly higher blood pressure in relationship with the progression of renal failure in all the patients of this group.

As shown in Figure 3, the probability of renal survival without chronic dialysis (censoring death without chronic dialysis) was significantly higher in group II patients, who received immunosuppressive treatment: four years after the onset of renal function decline it was 90%, in comparison with a probability of 55% in group I, who was conservatively managed ($P < 0.01$). After seven years of follow-up these probabilities were 90% and 20%, respectively ($P < 0.01$). Patient survival four years after the onset of renal insufficiency was 84% in group II and 78% in group I patients (P = NS). After seven years of follow-up, these probabilities were 84% and 63%, respectively (P = NS). At the end of the follow-up period, 11 patients (58%) of group II maintained a S_{Cr} ≤1.5 mg/dL, whereas all the patients of group I showed a S_{Cr} ≥1.5 mg/dL. There were significant differences between both groups in the slope of $1/S_{Cr}$ (group I −0.0109 ± 0.0086 dL/mg/month; group II 0.0073 ± 0.0201 dL/mg/month, $P < 0.01$) and the slope of C_{Cr} (group I −1.1872 ± 1.5027 mL/m/month; group II 0.4916 ± 1.7019 mL/m/month, $P < 0.01$).

Table 3 shows that there were no significant differences between those patients of group II with a S_{Cr} ≤1.5 mg/dL at the end of the follow-up (N = 11) and the remaining 8 patients with S_{Cr} ≥1.5 mg/dL. Mean S_{Cr} at the onset of immunosuppressive treatment was even higher (2.7 ± 1 vs. 1.8 ± 0.3 mg/dL) in patients with a later favorable evolution. Mean interval between renal biopsy and the onset of renal derangement was almost twice as much among the eight treated patients with a later evolution toward renal insufficiency (18.6 ± 18 vs. 10.7 ± 19.1 months) and the proportion of males higher (6/2 vs. 5/6; Table 3), but these differences did not reach statistical significance. There were significant differences between group II patients with a favorable evolution and those with progression to renal insufficiency in the slope of $1/S_{Cr}$ (0.0171 ± 0.0214 vs. −0.0061 ± 0.0049 dL/mg/month; $P < 0.05$) and in the slope of C_{Cr} (1.2903 ± 1.7230 vs. −0.6065 ± 0.9092 mL/m/month; $P < 0.05$).

A relapse of nephrotic-range proteinuria with renal function deterioration was observed in two patients; both of them had achieved a partial remission with recovery of a normal renal function after the first course of immunosuppressive treatment. They were treated with a second course of prednisone and chlorambucil at the same doses of the first course. One of the patients showed a recovery of normal renal function (S_{Cr} 1.1 mg/dL at the last visit) with a reduction of proteinuria to a non-nephrotic range. The other patient did not show proteinuria reduction with the treatment and his S_{Cr} is 2.5 mg/dL one year after the end of the second course of immunosuppressive treatment.

The most important complications of immunosuppressive treatment administered to group II patients are shown in Table 4. All these complications appeared after the fourth month of treatment. The two cases of *Pneumocystis carinii* pneumonia showed a typical syndrome of severe dyspnea and extensive lung involvement on x-ray film of the thorax. The diagnosis was established by the demonstration of *Pneumocystis* on bronchopulmonary lavage. Both patients evolved satisfactorily with appropriate treatment (trimethoprim-sulfametoxazole), although one of them needed assisted ventilation for two weeks.

DISCUSSION

Our study shows that immunosuppressive treatment (oral prednisone for 6 months plus oral chlorambucil administered concurrently for 3½ months) of patients with MGN and deteriorating renal function is a better therapeutic regimen than merely a conservative approach. Whereas all of the conservatively treated patients showed a progression of renal insufficiency, renal function improved and proteinuria decreased in a considerable number of patients treated with prednisone and chlorambucil: at the end of follow up (51.8 ± 36.5 months) more than a half of the actively treated patients maintained a serum creatinine lower than 1.5 mg/dL. The probability of renal survival without chronic dialysis was significantly higher among patients who received immunosuppressive therapy (90% after 7 years of follow-up) in comparison with patients treated with a conservative approach (20%

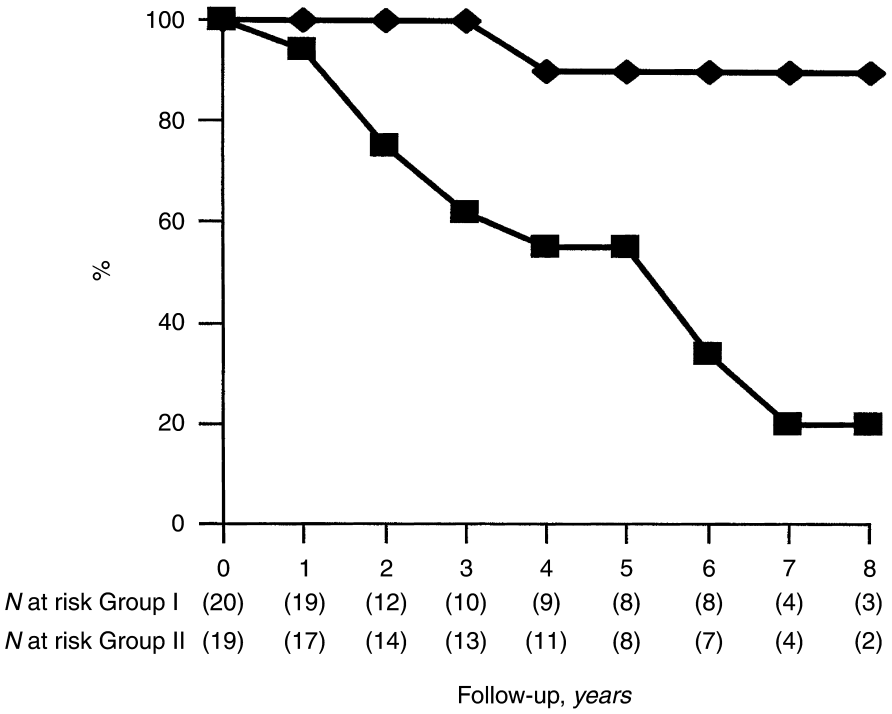

Fig. 3. Probability of renal survival in group I (no treatment; ■) and group II (immunosuppressive treatment; ◆).

Table 3. Clinical features at the onset of immunosuppressive treatment in group II patients with favorable (recovery of normal renal function) or unfavorable (renal insufficiency at the end of follow-up) response to treatment

	Normal renal function (S_{Cr} <1.5 mg/dL) $N = 11$	Renal insufficiency (S_{Cr} >1.5 mg/dL) $N = 8$	P
Age *years*	59 ± 19 r = 26–81	50 ± 21 r = 24–77	NS
Gender *M/F*	5/6	6/2	NS
Interval between biopsy and onset of immunosuppressive treatment *months*	10.7 ± 19.1 r = 0–65	18.6 ± 18 r = 2–43	NS
S_{Cr} *mg/dL*	2.7 ± 1 r = 1.5–5.2	1.8 ± 0.3 r = 1.6–2.5	NS
Proteinuria *g/24 h*	11.1 ± 3.1 r = 7.2–15	11.3 ± 4.1 r = 7.8–21	NS
MAP *mm Hg*	101 ± 10 r = 86–116	98 ± 11 r = 76–113	NS
Stage of MGN	2 ± 0.6 r = 1–3	2 ± 0.5 r = 1–3	NS
Interstitial fibrosis	1.3 ± 0.5 r = 1–2	1.2 ± 0.4 r = 1–2	NS
Follow-up *months*	46 ± 39 r = 18–120	59 ± 32 r = 8–117	NS

Table 4. Complications of immunosuppressive treatment

	Number of patients
Pneumocystis carinii pneumonia	2 (10.5%)
Herpes zoster	4 (21%)
Steroid psychoses	1 (5.2%)
Steroid diabetes	1 (5.2%)
Avascular bone necrosis	1 (5.2%)

after 7 years of follow-up). Nephrotic-range proteinuria persisted in all the patients with a conservative management until they reached end-stage renal failure. Five (25%) of them died during the follow-up. The high mortality and the causes of death illustrate well that a sustained nephrotic syndrome is a high-risk condition for cardiovascular and infectious complications.

Previous studies have shown that approximately 50 to 60% of patients with idiopathic MGN never develop end-stage renal failure and almost a half of these may have a spontaneous remission [6–11]. In one study 73% of untreated MGN patients retained adequate renal function after eight years [2], and based on these results, the authors did not recommend the use of steroids or immunosuppressive agents for this entity. However, our results show that in the subgroup of patients with a progressive renal insufficiency (31.9% in our experience) a course of immunosuppressive therapy can avoid or delay the progression to end-stage renal failure, in comparison with the uniform progression of untreated patients.

Another widely used therapeutic approach consists in the administration of steroids and alkylating agents (chlorambucil being the most commonly used) to patients with MGN and nephrotic syndrome before the appearance of renal dysfunction. Studies from Ponticelli and collaborators have shown a long-term favorable influence of this therapy when compared to non-treated patients [3–5]. The rationale for this early aggressive

treatment (most patients with MGN present with nephrotic syndrome) is that a persistent massive proteinuria would induce progressive tubulointerstitial damage, even in those patients with a normal renal function maintained over several years. According to this hypothesis, when renal dysfunction appears, the presence of such interstitial fibrosis would render any aggressive therapy ineffective. However, several criticisms may be raised against this approach: first, the appearance of renal insufficiency is a relatively early event in MGN patients with an unfavorable evolution; in our study, the mean interval between renal biopsy and appearance of renal dysfunction was 10.8 ± 11.8 months in the first period and 14 ± 18.6 months in the second, ranging from 0 to 65 months. Our findings corroborate that of previous studies [6], showing that patients with a progressive course usually manifest decline of renal function within the first two years of evolution. Most of spontaneous partial or complete remissions also appear within the first two or three years of initial diagnosis [6]. Therefore, only a few cases maintain nephrotic-range proteinuria for more than two to three years without clinical evidence of spontaneous improvement or renal function decline.

Another criticism against the early aggressive therapeutic approaches is that many patients who would spontaneously evolve into complete or partial remissions are included in immunosuppressive therapies. Although male sex and massive sustained proteinuria are associated with a poorer prognosis, only the appearance of a steady decline of renal function could be considered as a constant predictor of a poor outcome. Once renal function starts to decline, a progressive course toward end-stage renal disease ensues in almost all patients, as our untreated patients of group I exemplify.

On the other hand, immunosuppressive therapy is not without serious risks, as several previous studies have emphasized [19, 22, 23, 25, 26]. Our experience is in accordance with this general warning: although the total number of serious complications was relatively low, some of them were particularly severe; two of our patients suffered a *Pneumocystis carinii* infection, which fortunately resolved with trimethoprim-sulphametoxazole treatment. We have not found previous reports of *Pneumocystis carinii* infection in patients with nephrotic syndrome, although the number of respiratory infections as a complication of immunosuppressive therapies in MGN with renal insufficiency was high in some studies [19, 20]. Our two cases illustrate how the combination of nephrotic syndrome plus immunosuppressive therapy leads the patient to a severe immunodeficiency with the risk of very dangerous complications. Since the diagnosis of these two *Pneumocystis* pneumonia cases, we introduced into our protocol a prophylaxis with trimethoprim-sulphametoxazole for every actively treated MGN patient, and no new cases of *Pneumocystis* infection have appeared.

All of these reasons taken together (early evolution of most patients toward spontaneous remission or progressive renal derangement, high rate of spontaneous remissions, and serious secondary effects of immunosuppressive therapies), several groups have opted to reserve aggressive treatment for patients who have early evidence of renal impairment. Several studies have reported a beneficial influence of different immunosuppressive strategies in patients with deteriorating renal function [17–25]. However, comparison with the long-term outcome of untreated patients, as our study presents, had not been performed yet.

Alternating monthly cycles of steroids and chlorambucil for six months, based on the scheme of Ponticelli and collaborators [17, 22], oral cyclophosphamide and steroids for one to two years [18, 21], low-dose oral azathioprine plus steroids for very prolonged periods [23], and cyclosporine [27] have been reported to favorably influence the course of idiopathic MGN with a progressive renal function decline. One exception for these general favorable results is the use of monthly intravenous cyclophosphamide, which has been shown to be ineffective [20, 24]. We arbitrarily chose a modification of the Ponticelli protocol, using a concurrent, non-alternating administration of oral steroids (progressively tapered for 6 months) and oral chlorambucil (0.15 mg/kg/day for 14 weeks). This regimen is administered more easily than the alternating protocol that also includes intravenous boluses of methylprednisolone [3–5].

Information about clinical characteristics at the onset of treatment that could influence the response to these immunosuppressive regimens in MGN with deteriorating renal function is scarce. When we compared those cases of group II (who received prednisone plus chlorambucil) with a favorable response (11 out of 19 patients, 58%) and the remaining 8 patients (42%) whose disease evolved into chronic renal failure, no significant differences were observed (Table 3). However, it should be emphasized that the interval between renal biopsy and the onset of renal function decline was almost twice as much among the eight patients with an unfavorable evolution. Conceivably, a longer period of massive proteinuria could induce a progressive tubulointerstitial fibrosis [28] that, once renal function starts to decline, would preclude a satisfactory long-term response to aggressive therapies. If this hypothesis is correct, immunosuppressive therapy could be indicated in MGN patients with nephrotic syndrome lasting for more than 12 to 24 months, even in the absence of a decline in renal function. Another possible explanation could rely on the presence of reversible functional factors in the patients with a favorable response. Nevertheless, factors such as overzealous diuretic therapy or acute impairments of renal function induced by ACE inhibitors or NSAIDs were

carefully ruled out in every patient before the onset of immunosuppressive treatment.

Our study has the limitations of a retrospective cohort study. Drugs such as ACE inhibitors and statins, that have demonstrated a beneficial effect on the progression of renal insufficiency and the appearance of cardiovascular events, are commonly proscribed in patients with MGN and nephrotic syndrome. Earlier group I patients (period 1975 to 1989) did not receive these treatments (available from the eighties) and this fact could influence their renal insufficiency progression rate. However, the homogeneity of both groups (conservative and immunosuppressive treatments) should be stressed in terms of clinical and biochemical findings at the time of renal biopsy, as well as the similar evolution until the appearance of renal insufficiency (Table 1). In addition, the regular and long-term follow-up obtained in every patient allowed us to accurately analyze the long-term outcome of renal function and possible delayed side effects of immunosuppressive treatment. Based on our findings, we recommend the following policy for idiopathic MGN patients: close monitoring of renal function should be performed in those patients with nephrotic syndrome and normal renal function, taking into account that both spontaneous remissions and onset of renal function decline appear within the first two years of evolution in the majority of cases. Conservative measures, including salt restriction, diuretics and statins should be the fundamental therapeutic approach at this stage of the disease; in addition, we believe that an attempt to reduce proteinuria with ACE inhibitors should be tried in every case [29–31], even in normotensive patients, unless specific contraindications for these drugs are indicated. In those patients who develop renal insufficiency (always accompanied by nephrotic massive proteinuria in our experience), a course of immunosuppressive treatment should be administered as early as possible, once the presence of functional factors is ruled out as precipitating factors of renal function derangement. Our study shows that this selective immunosuppressive therapy rescues a considerable proportion of patients who, if untreated, without exception would evolve into advanced chronic renal failure.

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REFERENCES

1. Muirhead N: Management of idiopathic membranous nephropathy: Evidence-based recommendations. *Kidney Int* 55(Suppl70): S47–S55, 1999
2. Schiepatti A, Mosconi L, Perna A, *et al*: Prognosis of untreated patients with idiopathic membranous nephropathy. *N Engl J Med* 329:85–89, 1993
3. Ponticelli C, Zucchelli P, Imbasciati E, *et al*: Controlled trial of methylprednisolone and chlorambucil in idiopathic membranous nephropathy. *N Engl J Med* 310:946–950, 1984
4. Ponticelli C, Zucchelli P, Passerini IP, *et al*: Methylprednisolone plus chlorambucil as compared with methylprednisolone alone for the treatment of idiopathic membranous glomerulopathy. *N Engl J Med* 327:599–603, 1992
5. Ponticelli C, Zucchelli P, Passerini IP, *et al*: A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. *Kidney Int* 48:1600–1604, 1995
6. Donadio JV, Torres VE, Velosa JA, *et al*: Idiopathic membranous nephropathy: The natural history of untreated patients. *Kidney Int* 33:708–715, 1988
7. Davidson AM, Cameron JS, Kerr DNS, *et al*: The natural history of renal function in untreated idiopathic membranous glomerulonephritis in adults. *Clin Nephrol* 22:61–67, 1984
8. Glassock RJ: The therapy of idiopathic membranous glomerulonephritis. *Semin Nephrol* 11:138–147, 1991
9. Ramzy MH, Cameron JS, Turner DR, *et al*: The long-term outcome of idiopathic membranous nephropathy. *Clin Nephrol* 16:13–19, 1981
10. Noel LH, Zanetti M, Droz D, Barbanel C: Long-term prognosis of idiopathic membranous glomerulonephritis. Study of 116 untreated patients. *Am J Med* 66:82–89, 1979
11. Zucchelli P, Ponticelli C, Cagnoli L Passerini P: Long-term outcome of idiopathic membranous nephropathy with nephrotic syndrome. *Nephrol Dial Transplant* 2:73–78, 1987
12. Honkanen E, Törnroth T, Grönhagen-Riska C, Sankila R: Long-term survival in idiopathic membranous glomerulonephritis: Can the course be clinically predicted? *Clin Nephrol* 41:127–134, 1994
13. Pei Y, Cattran D, Greenwood C: Predicting chronic renal insufficiency in idiopathic membranous glomerulonephritis. *Kidney Int* 42:960–966, 1992
14. Reichert LJ, Koene RA, Wetzels JF: Prognostic factors in idiopathic membranous nephropathy. *Am J Kidney Dis* 31:1–11, 1998
15. Cattran D, Pei Y, Greenwood C, *et al*: Validation of a predictive model of idiopathic membranous nephropathy: Its clinical and research implications. *Kidney Int* 51:901–907, 1997
16. Marx BE, Marx M: Prognosis of idiopathic membranous nephropathy: A methodolical meta-analysis. *Kidney Int* 51:873–879, 1997
17. Mathieson PW, Turner AM, Maidment CGH, *et al*: Prednisolone and chlorambucil treatment in idiopathic membranous nephropathy with deteriorating renal function. *Lancet* 2:869–872, 1988
18. Jindal K, West M, Bear R, Goldstein M: Long-term benefits of therapy with cyclophosphamide and prednisone in patients with membranous glomerulonephritis and impaired renal function. *Am J Kidney Dis* 19:61–67, 1992
19. Branten AJW, Reichert LJM, Koene RAP, Wetzels JFM: Oral cyclophosphamide versus chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency. *Quart J Med* 91:359–366, 1998
20. Reichert LJM, Huysmans FT, Assmann K, *et al*: Preserving renal function in patients with membranous nephropathy: Daily oral chlorambucil compared with intermittent monthly pulses of cyclophosphamide. *Ann Intern Med* 121:328–333, 1994
21. Bruns FJ, Adler S, Fraley DS, Segel DP: Sustained remission of membranous glomerulonephritis after cyclophosphamide and prednisone. *Ann Intern Med* 114:725–730, 1991
22. Warwick GL, Geddes CG, Boulton-Jones JM: Prednisolone and chlorambucil therapy for idiopathic membranous nephropathy with progressive renal failure. *Quart J Med* 87:223–229, 1994
23. Bone JM, Rustom R, Williams PS: "Progressive" versus "indolent" idiopathic membranous glomerulonephritis. *Quart J Med* 90:699–706, 1997
24. Falk RJ, Hogan SL, Muller KE, *et al*: Treatment of progressive membranous glomerulopathy. A randomized trial comparing cyclophosphamide and corticosteroids with corticosteroids alone. *Ann Intern Med* 116:438–445, 1992
25. Wetzels JFM, Reichert LJM: Efficacy of immunosuppressive treatment in patients with membranous nephropathy and renal insufficiency. *Kidney Int* 52(Suppl 61):S63–S66, 1997
26. Imperiale TF, Goldfarb S, Berns JS: Are cytotoxic agents beneficial in idiopathic membranous nephropathy? A meta-analysis of the controlled trials. *J Am Soc Nephrol* 5:1553–1558, 1995
27. Cattran DC, Greenwood C, Ritchie S, *et al*: A controlled trial of cyclosporine in patients with progressive membranous nephrop-

athy: Canadian Glomerulonephritis Study Group. *Kidney Int* 47: 1130–1135, 1995
28. Remuzzi G, Bertani T: Pathophysiology of progressive nephropathies. *N Engl J Med* 339:1448–1456, 1998
29. Praga M, Hernández E, Montoyo C, *et al*: Long-term beneficial effects of angiotensin-converting enzyme inhibition in patients with nephrotic proteinuria. *Am J Kidney Dis* 20:240–248, 1992
30. Praga M, Paz-Artal E, Hernández E, *et al*: Antiproteinuric effect of angiotensin-converting enzyme inhibition and C5b-9 urinary excretion in membranous glomerulonephritis. *Nephrol Dial Transplant* 12:2576–2579, 1997
31. Gansevoort RT, Heeg JE, Vriesendorp R, *et al*: Antiproteinuric drugs in patients with idiopathic membranous glomerulopathy. *Nephrol Dial Transplant* 7(Suppl 1):91–96, 1992